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New apotirucallane-type triterpenoids from *Chisocheton paniculatus*

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Abstract: Two new apotirucallane triterpenoids, namely chisiamols G (**1**) and H (**2**), featuring a 21,23-lactone, together with five known triterpenoids, were isolated from the twigs of *Chisocheton paniculatus*. The structures of the new compounds were elucidated on the basis of spectroscopic and chemical methods.

Keywords: Chisocheton paniculatus, apotirucallane triterpenoids, chisiamols G and H

Introduction

The genus *Chisocheton* (Meliaceae) comprising about 50 species is mainly distributed in India and Malaysia, which is traditionally used to treat stomach and kidney problems, backache, fever, rheumatism and malaria. *Chisocheton paniculatus* is the only species growing in southern China.[1] Phytochemical studies of genus *Chisocheton* have led to the isolation of sesquiterpenoids, triterpenoids and limonoids, some of which showed anti-inflammatory, anti-feedant, anti-fungal and cytotoxic activities. Previous phytochemical investigation on *C. paniculatus* resulted mainly in the isolation of apotirucallane-type triterpenoids.[2] In the present study, two new apotirucallane triterpenoids, named chisiamols G (**1**) and H (**2**), together with five known triterpenoids, chisiamol A (**3**),[2m] sapelin B (**4**),[3] 3α-acetoxy-21,24*R*-epoxyapotirucall-14-ene-7α,23*R*,25-triol (**5**),[2m] chisiamol B (**6**),[2m] and 3α-acetoxy-21,23-epoxyapotirucall-14-ene-7α,21*R*,24,25-tetrol (**7**)[2m] were isolated from the leaves and stems of *C. paniculatus* (Figure 1). Herein, we describe the isolation and structural elucidation of these new compounds.

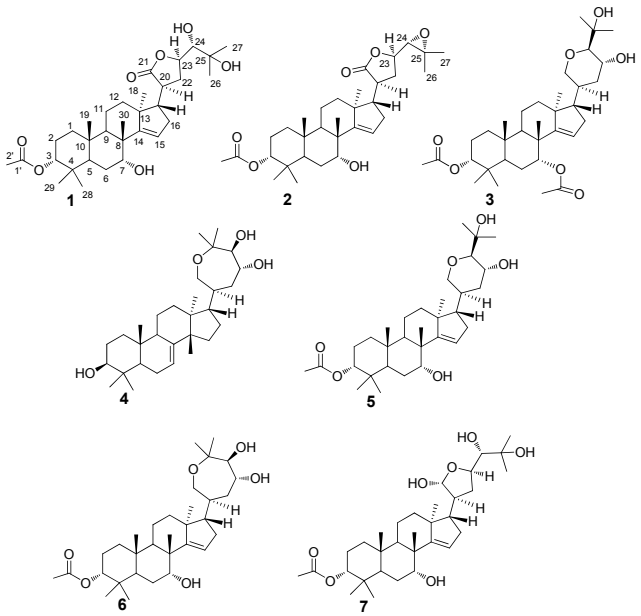

Figure 1. Chemical structures of compounds **1**–**7**

Results and Discussion

Compound **1** was obtained as a white amorphous powder. Its molecular formula was determined to be $C_{32}H_{50}O_7$ by HRESIMS *m/z* $[M + Na]^+$ 569.3458 (calcd for $C_{32}H_{50}O_7Na$, 569.3454). The IR absorptions at 3448, 1720 and 1630 cm^{-1} indicated the presence of hydroxyl, ester carbonyl, and double bond groups, respectively. The ^1H NMR spectrum showed seven tertiary methyls at δ_H 0.85, 0.93, 0.96, 1.09, 1.12, 1.24, and 1.28 (each 3H, s), one acetyl methyl at δ_H 2.06 (3H, s), one olefinic proton at δ_H 5.45, and four proton signals at δ_H 3.26 (d), 3.95 (br. s), 4.66–4.74 (m), and 4.63 (br. s) attributable to the protons of oxygenated methines (Table 1). All the 32 carbon resonances were resolved in the ^{13}C NMR spectrum, and further classified by DEPT and HSQC experiments as eight methyls, seven sp^3 methylenes, eight sp^3 methines (four oxygenated), five sp^3 quaternary carbons (one

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Table 1. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR data of 1 and 2 (CD_3OD)

position	chisiamol G (**1**)		chisiamol H (**2**)	
	δ_H	δ_C	δ_H	δ_C
1α	1.22–1.30, m	35.0, CH_2	1.25–1.32, m	35.0, CH_2
1β	1.33–1.42, m		1.36–1.46, m	
2α	1.50–1.57, m	24.3, CH_2	1.52–1.62, m	24.3, CH_2
2β	1.87–1.99, m		1.91–1.98, m	
3	4.63, br. s	80.3, CH	4.62, br. s	80.3, CH
4		37.8, C		37.8, C
5	1.97–2.09, m	43.6, CH	1.99–2.11, m	43.6, CH
6α	1.61–1.67, m	26.0, CH_2	1.62–1.73, m	26.0, CH_2
6β	1.72–1.80, m		1.76–1.83, m	
7	3.95, br. s	74.4, CH	3.95, br. s	74.4, CH
8		45.7, C		45.7, C
9	1.97–2.09, m	43.7, CH	1.99–2.11, m	43.7, CH
10		39.3, C		39.3, C
11α	1.48–1.53, m	18.0, CH_2	1.53–1.58, m	18.0, CH_2
11β	1.67–1.73, m		1.71–1.77, m	
12	2.09–2.18, m	34.3, CH_2	2.15–2.22, m	34.4, CH_2
13		48.5, C		48.5, C
14		162.2, C		162.3, C
15	5.45, d (1.7)	120.8, CH	5.46, d (2.3)	120.6, CH
16α	2.28–2.35, m	33.6, CH_2	2.28–2.34, m	33.8, CH_2
16β	1.99–2.08, m		2.04–2.12, m	
17	2.15–2.22, m	56.2, CH	2.15–2.22, m	56.1, CH
18	1.09, s	20.8, CH_3	1.09, s	20.7, CH_3
19	0.96, s	16.4, CH_3	0.96, s	16.4, CH_3
20	2.81–2.90, m	41.6, CH	2.95, ddd (5.7, 8.4, 12.0)	41.6, CH
21		181.6, C		181.0, C
22α	2.18–2.33, m	32.5, CH_2	2.45, ddd (6.5, 8.6, 12.6)	31.7, CH_2
22β	2.18–2.33, m		1.99–2.06, m	
23	4.66–4.74, m	79.1, CH	4.26, ddd (5.7, 7.4, 10.5)	80.6, CH
24	3.26, d (1.9)	79.5, CH	2.86, d (8.1)	66.4, CH
25		73.9, C		59.4, C
26	1.24, s	25.3, CH_3	1.34, s	19.9, CH_3
27	1.28, s	28.5, CH_3	1.34, s	25.4, CH_3
28	0.93, s	22.8, CH_3	0.92, s	22.8, CH_3
29	0.85, s	28.6, CH_3	0.85, s	28.6, CH_3
30	1.12, s	29.3, CH_3	1.10, s	29.3, CH_3
3-OAc		173.2, C		173.2, C
	2.06, s	21.7, CH_3	2.06, s	21.7, CH_3

oxygenated), two ester carbonyls (δ_C 173.2 and 181.6), and one trisubstituted double bond (δ_C 120.8 and 162.2) (Table 1). Careful analysis of its ^{1}H and ^{13}C NMR data indicated that the NMR data of **1** highly resembled those of the co-existing compound 3α-acetoxy-21,23-epoxyapotirucall-14-ene-7α,21*R*,24,25-tetrol (**7**)[2m] except for the absence of both the proton and carbon signals of the hemiacetal group (δ_C 96.5; δ_H 5.29), and the presence of an additional ester carbonyl, suggesting that C-21 hemiacetal in **7** was oxygenated to a lactone group (δ_C 181.6) in **1**. To prove this speculation, an HMBC experiment was performed, in which, the ester carbonyl was placed at C-21 by the correlations from H_2-22 (δ_H 2.18–2.33) and H-20 (δ_H 2.81–2.90) to C-21 (δ_C 181.6). This was supported by ^{1}H-^{1}H COSY spectrum, in which, a proton bearing structural fragment from C-17 to C-24 as depicted in bold bond (Figure 2) was revealed. In addition, the key HMBC correlations from H-3 (δ_H 4.63) to C-1′ (δ_C 173.2) assigned an acetoxy group at C-3; the HMBC correlations of Me-30 (δ_H 1.12)/C-7 (δ_C 74.4), and H-7 (δ_H 3.95)/C-6 located a hydroxyl group at C-7 (Figure 2).

In the ROESY spectrum of **1**, the correlations of Me-19/H-3, Me-29/H-3, Me-19/Me-30, and Me-30/H-7, indicated that Me-19, Me-29, Me-30, H-3, and H-7 were cofacial and were randomly assigned to be β-oriented. Subsequently, the ROESY correlations of H-20/H-23, and Me-18/H-20 indicated that they were α-oriented (Figure 4). The small coupling constant (1.9 Hz) between H-23 and H-24 indicated that they were in a *gauche* relationship, showing that H-24 was β-oriented.[4]

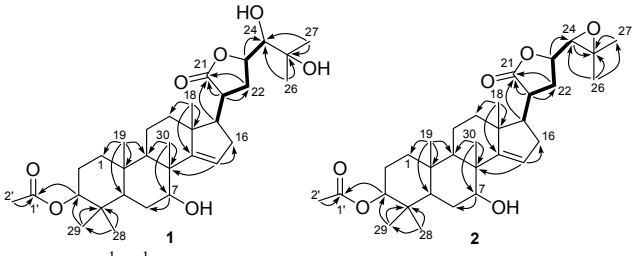

Figure 2. ^{1}H-^{1}H COSY (bold lines) and key HMBC (H→C) correlations of **1** and **2**

The structure of compound **1** was further verified by chemical correlation with the coexisting known compound **7**. Both compounds **1** and **7** were treated with $LiAlH_4$ to afford a common compound **8** (Figure 3),[5] confirming the structural assignment for compound **1**. The structure of **8** was assigned as the reduced derivative of compound **7** based on the spectroscopic data. In the ESIMS, the $[M + Na]^+$ peak at *m/z* 531.4, $[2M + Na]^+$ peak at *m/z* 1039.7 and $[M + HCOO]^-$ peak

at *m/z* 553.7 were all consistent with the molecular formula $C_{30}H_{52}O_6$ of **8** with six hydroxyl groups. A comparison of ^{1}H NMR spectra of **7** and **8** was particularly informative. The absence of the acetyl methyl (δ_H 2.06 in **7**) and the upfield shifted H-3 at δ_H 3.33 (δ_H 4.63 in **7**) of **8** indicated the presence of OH-3 in **8**. The remaining two hydroxyls in **8** were assigned to C-21 and C-23 by the chemical shifts of H_2-21 at δ_H 3.45 and δ_H 3.77 (each 1H, J = 11.0 Hz) and H-23 at δ_H 4.08, respectively.

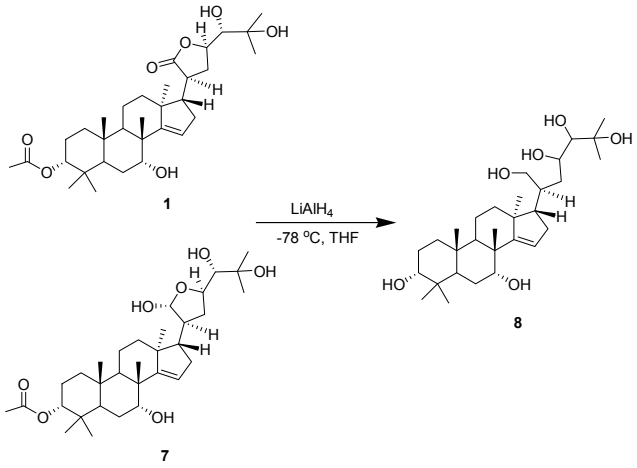

Figure 3. Reduction of compounds **1** and **7** to afford **8**

Hence, the structure of **1**, namely chisiamol G, was assigned as 3α-acetoxy-7α,24,25-trihydroxyl-21,23-epoxyapotirucall-14-ene-21-one, an apotirucallane-type triterpenoid possessing a five-membered lactone formed between C-21 and C-23.

Compound **2** was obtained as a white amorphous powder. Its molecular formula $C_{32}H_{48}O_6$ was assigned by HRESIMS at *m/z* $[M + Na]^+$ 551.3348 (calcd for $C_{32}H_{48}O_6Na$, 551.3349). Its IR spectrum exhibited absorption bands for hydroxyl (3432 cm^{-1}), ester carbonyl (1724 cm^{-1}), and double bond (1630 cm^{-1}) functionalities. A comparison of the ^{13}C NMR spectra (Table 1) of compounds **1** and **2** revealed that their structures were close related, except for that two oxygenated carbon signals at δ_C 79.5 (C-24) and at δ_C 73.9 (C-25) in **1** were significantly upfield shifted to δ_C 66.4 (C-24) and δ_C 59.4 (C-25) in **2**, respectively**,** suggesting that an 24,25-epoxide ring was present in **2** instead of the 24,25-diol motif in **1**. This was consistent with the fact that the molecular weight of **2** was 18 mass units less than that of **1**, and was further supported by the almost identical chemical shifts of C-24 and C-25 of **2** as compared with those of 7α-hydroxyl-21α-acetoxy-21,23-epoxyapotirucall-24,25-epoxide-14-ene-3-one and 3α,7α-dihydroxyl-21α-acetoxy-21,23-epoxyapotirucall-24,25-epoxide-14-ene, both of which possessing an 24,25-epoxide were respectively reported as compounds A and D in the literature.[2a] The structure of **2** was finally confirmed by 2D NMR spectra, especially HMBC (Figure 2) and ROESY (Figure 4) spectra. In the ROESY experiment, the correlations of Me-29/H-3, Me-19/Me-30, and Me-30/H-7, indicated that Me-19, Me-29, Me-30, H-3, and H-7 were cofacial and were randomly assigned to be β-oriented. Furthermore, the ROESY correlations of H-20/H-23, and Me-18/H-20 indicated that Me-18, H-20, and H-23 were cofacial and α-oriented. The 24,25-epoxide ring was assigned to be α-directed by the ROESY correlations of H-22α/H-23 and H-22β/H-24 (Figure 4).[6] The chemical shifts of C-24 (δ_C 66.4) and C-25 (δ_C 59.4), and the coupling constant ($J_{23,24}$ = 8.1 Hz) between H-23α and H-24 further supported the α-orientation of the epoxide in **2** as compared with the corresponding data of the bruceajavanones A–E.[6] The structure of **2** was thus established as 3α-acetoxy-7α-hydroxyl-21,23-epoxyapotirucall-24,25-epoxide-14-ene-21-one, namely chisiamol H.

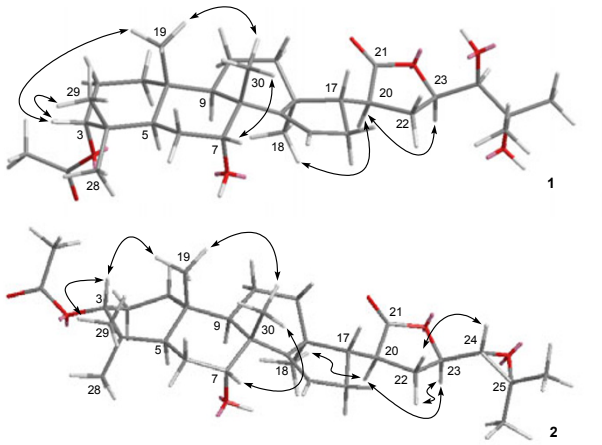

Figure 4. Key NOE (H↔H) correlations of **1** and **2**

All isolated compounds (**1**–**7**) were tested in an anti-microbial assay against *Helicobacter pylori*-SS1 *in vitro* according to standard protocols, in which Minimum inhibitory concentration (MIC) > 100 μg/mL was defined as inactive[7], and metronidazole (Shanghai Henshan Pharmaceutical Company, Ltd. with a purity of 99%; MIC = 0.312 μg/mL) was used as the positive control. However, none of these compounds showed activity (MIC > 50 μg/mL).

Experimental Section

General Experimental Procedures. Optical rotations were measured with a Perkin-Elmer 341 polarimeter. UV spectra were measured on a Shimadzu UV-2550 spectrophotometer. IR spectra were recorded on a Perkin-Elmer 577 spectrometer using KBr disks. NMR spectra were measured on a Bruker AM-400 spectrometer. ESIMS was carried out on a Finnigan LCQ-DECA instrument, and HRESIMS spectra were made on a Bruker Daltonics micrOTOFQII or a Waters-Micromass Q-TOF Ultima Global electrospray mass spectrometer. All solvents used were of analytical grade (Shanghai Chemical Reagents Company, Ltd.). Different absorbents were employed for column chromatography: silica gel (200–300 mesh) and silica gel H (Qingdao Haiyang Chemical Co. Ltd.); RP-18 reversed silica gel (150–200 mesh, Merck); MCI gel (CHP20P, 75–150 ím, Mitsubishi Chemical Industries Ltd.); Sephadex LH-20 gel (Amersham Biosciences). Fractions were monitored by TLC (silica gel GF254, 0.25 mm, Merck), and spots were visualized by heating silica gel plates sprayed with 10% H_2SO_4 in ethanol. Semipreparative HPLC was performed on a Waters 1525 pump equipped with a Waters 2489 detector

and an YMC-Pack ODS-A column (10 × 250 mm, S-5 μm, 12 nm).

Plant Materal. The leaves and stems of *C. paniculatus*, were collected in Mengla County, Yunnan Province of China in September of 2009, and the plant was identified by Professor You-Kai Xu of Xishuangbanna Tropical Botanical Garden, Chinese Academy of Sciences. A voucher specimen (accession number CS-2009-2Y) has been deposited in the Shanghai Institute of Materia Medica, Chinese Academy of Sciences.

Extraction and Isolation. Dried leaves and stems of *C. paniculatus* (6 kg) were extracted by 95% EtOH at room temperature. The crude extract (70 g) was dissolved in H_2O (500 mL) and then extracted with EtOAc (200 mL × 3). The EtOAc extract (24 g) was subjected to an MCI column (75−150 μm, 8 × 30 cm, MeOH/H_2O, 50:50 to 90:10, v/v) to give fractions E–K. Fraction I (1.80 g) was chromatographed on a silica gel column eluted with petroleum ether/Me_2CO (300–400 mesh, 4 × 20 cm, 10:1 to 4:1) to yield four fractions (I1–4). Fraction I4 (193 mg) was subjected to a silica gel column (300–400 mesh, 3 × 18 cm, CH_2Cl_2/MeOH, 150:1, 100:1, 70:1, 50:1, 30:1, 20:1, 10:1) to give four fractions (I4a–d). Purification of fraction I4b (30 mg) by a RP-18 silica gel column (150–200 mesh, 3 × 15 cm, MeOH/H_2O, 70:30 to 80:20) gave **1** (20 mg). Fraction J (5.50 g) was chromatographed on a silica gel column eluted with petroleum ether/Me_2CO (300–400 mesh, 8 × 20 cm, 10:1 to 6:1) to yield seven fractions (J1–7). Fraction J3 (221 mg) was submitted to a silica gel column (300–400 mesh, 3 × 20 cm, CH_2Cl_2/MeOH, 100:1, 80:1, 60:1) to give three fractions (J3a–c). Purification of fraction J3a (12 mg) with Sephadex LH-20 (3 × 100 cm, EtOH) yielded **2** (3 mg). Fraction J3b (73 mg) was applied to a RP-18 silica gel column (150–200 mesh, 3 × 15 cm, MeOH/H_2O, 80:20 to 90:10) to give fractions J3b1 and J3b2. Fraction J3b2 (14 mg) was further purified by preparative HPLC (eluting with MeCN/H_2O, 85:15 to 95:5, from 0 to 20 min, 3 mL/min) afforded **3** (3 mg). Purification of fraction J3c (15 mg) by preparative HPLC (eluting with MeCN/H_2O, 90:10 to 95:5, from 0 to 20 min, 3 mL/min) yielded **4** (4 mg). Fraction J5 (358 mg) and J6 (293 mg) were subjected to a silica gel column (300–400 mesh, 3 × 20 cm, petroleum ether/EtOAc, 10:1, 8:1, 6:1, 4:1) to give two corresponding fractions J5a–b and J6a–b, respectively. Fraction J5a (140 mg) and J6a (255 mg) were applied to a silica gel column (300–400 mesh, 3 × 18 cm, CH_2Cl_2/MeOH, 100:1, 80:1, 60:1, 40:1) to give three corresponding fractions J5a1–3 and J6a1–3, respectively. Purification of fractions J5a2 (40 mg) and J6a3 (83 mg) were subjected to RP-18 silica gel column (150–200 mesh, 3 × 15 cm, MeOH/H_2O, 90:10 to 100:0) to afford **5** (35 mg) and **6** (9 mg). Fraction E (1.34 g) was chromatographed on a silica gel column eluted with petroleum ether/Me_2CO (300–400 mesh, 6 × 20 cm, 10:1 to 1:1) to yield seven fractions (E1–7). Purification of fraction E3 (40 mg) was applied to RP-18 silica gel column (150–200 mesh, 3 × 15 cm, MeOH/H_2O, 80:20 to 90:10) to afford **7** (20 mg).

Chisiamol G (1): White amorphous powder; $[\alpha]_D^{23}$ – 105 (c = 0.27, MeOH); UV (MeOH) λ_{max} (log ε) 202.4 (4.3) nm; IR (KBr) ν_{max} 3448, 2939, 2871, 1765, 1720, 1630, 1458, 1385, 1169, 1034 cm^{-1}; ^1H NMR and ^{13}C NMR see Table 1; ESIMS m/z $[M + Na]^+$ 569.4; HRESIMS m/z $[M + Na]^+$ 569.3458 (calcd for $C_{32}H_{50}O_7Na$, 569.3454).

Chisiamol H (2): White amorphous powder; $[\alpha]_D^{23}$ – 69 (c = 0.30, MeOH); UV (MeOH) λ_{max} (log ε) 201.6 (4.15) nm; IR (KBr) ν_{max} 3432, 2937, 2871, 1774, 1724, 1630, 1458, 1385, 1250, 1188, 1024, 818 cm^{-1}; ^1H NMR and ^{13}C NMR see Table 1; ESIMS m/z $[M + Na]^+$ 551.4; HRESIMS m/z $[M + Na]^+$ 551.3348 (calcd for $C_{32}H_{48}O_6Na$, 551.3349).

Reduction of Compounds 1 and 7 with $LiAlH_4$. To a cooled solution (– 78 °C) of compound **1** or **7** (5.0 mg) in dry THF (2 mL), $LiAlH_4$ (3 mg) was added under nitrogen atmosphere. After stirring at the same temperature for 2 h, the reaction mixture was then allowed to r.t. and kept stirring overnight. After workup, the reaction mixture was diluted with H_2O (2 mL) and then extracted with EtOAc (3 × 5 mL). The combined organic phase were dried with anhydrous Na_2SO_4 and concentrated *in vacuo* to obtain the crude product, which was purified by a silica gel column eluted with CH_2Cl_2/MeOH (300–400 mesh, 3 × 12 cm, 50:1 to 10:1) to give compound **8** (about 3.0 mg).

Compound **8**: ESIMS m/z 531.4 $[M + Na]^+$, m/z 1039.7 $[2M + Na]^+$, m/z 553.7 $[M + HCOO]^-$; ^1H NMR (400 MHz, δ_H ppm, CD_3OD): 5.44 (H-15, d, J = 2.6 Hz), 4.08 (H-23, t, J = 6.7), 3.88 (H-17, t-like), 3.45, 3.77 (H-21, ABq, J = 11.0 Hz), 3.33 (H-3, t-like), 3.12 (H-24, d, 1.5 Hz).

Electronic Supplementary Material

Supplementary material is available in the online version of this article at http://dx.doi.org/ 10.1007/s13659-012-0065-5 and is accessible for authorized users.

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